REMARKS

These Remarks are responsive to the Office Action mailed August 4, 2009 in the above-referenced patent application. Claim 1 has been amended to be drawn to a "method for reducing hair growth in a female patient suffering from hirsutism comprising injecting an effective amount of botulinum toxin type A to the area situated between the lips and the nose of said patient." Claims 13–28 have been added. Applicant reserves the right to pursue cancelled subject matter in continuation or divisional patent applications. Support for these amendments can be found throughout the specification and in the claims as originally filed, for example page 1, lines 4–6, lines 20–26; page 2, line 2, lines 5–19, lines 24–33; and page 3, lines 1–10, lines 19–30. Further support for the claim as instantly presented is discussed below. Applicant respectfully requests entry of the above amendment and submits that the above amendment does not constitute new matter.

35 U.S.C. § 112, 1st para.— Written Description

Claims 1, 11, and 12 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicant respectfully traverses this rejection.

As a preliminary matter, Applicant submits that claim 1 has been amended to recite a "method for reducing hair growth in a female patient suffering from hirsutism comprising injecting an effective amount of botulinum toxin type A to the area situated between the lips and the nose of said patient." Applicant notes that the USPTO has acknowledged Applicant's support and enablement for this method twice in the Office Actions mailed November 20, 2007 and December 23, 2008 which both state that the specification is "...enabling for a method of treating or reducing hair growth in a patient suffering from hirsutism comprising administering an effective amount of botulinum toxin A to said person in need thereof..." To the extent that the rejection is applied to claim 1 as currently amended, Applicant submits the following remarks.

The Office Action correctly acknowledges the originally filed specification suggests reduction of downy hair growth: "...the specification as originally filed provides only for a method of reducing downy hair growth in a patient in want thereof comprising administering an

effective amount of botulinum toxin A to the upper lip of the patient." Office Action at page 3. Applicant concurs as reduction of hair growth is described throughout the specification and claims as originally filed. Moreover, the Example illustrates the reduction of downy hair growth in a patient. However, the Office Action asserts that the claim element "hirsutism" lack written description. Applicant respectfully disagrees that the claim element "hirsutism" is not described.

To satisfy the written description requirement, the specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Moreover, an Applicant may show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. M.P.E.P. § 2163.

Here, literal support for the claim element of a "method for reducing hair growth in a female patient suffering from hirsutism" may be found in the specification at least where it teaches "the use of botulinum toxin for the preparation of a medicament intended to prevent hair growth," "women with hirsutism," and "a patient suffering from hirsutism." Specification at page 1, lines 2, 4, 21, and 26; original claims 1 and 3.

Support for the claim element "injecting an effective amount of botulinum toxin type A" may be found in the specification at least where it teaches "Botulinum toxin, in particular botulinum toxin of type A (Dysport® marketed by Ipsen or Botox® marketed by Allergan)," "botulinum toxin," "botulinum toxin in an effective quantity," "administration of the botulinum toxin," "botulinum toxins of type A (including in particular A1 and A2)," "therapeutically effective quantity," "botulinum toxin of type A1," and "botulinum toxins of type A." Specification at page 1, lines 12–13, 20, 24; page 2, line 2, 6–18; page 3, line 18, 19–30; original claims 4 and 5.

Support for the claim element "the area situated between the lips and the nose" may be found in the specification at least where it teaches "the area situated between the lips and the nose [i.e. the white upper lip]." Specification at page 1, line 4; page 2, lines 24–28; page 3, lines 1–5; and original claim 9.

Finally, support for the claim element "shaving the area between the lips and the nose of the patient prior to administering the botulinum toxin" may be found in the specification at least

where it teaches that "method comprising the administration, to the area to be treated, of a pharmaceutical composition containing botulinum toxin in an effective quantity," "injection, to the areas of the patient effected by excessive hair growth...after these areas have been shaved," and "the area situated between the lips and the nose [i.e. the white upper lip]." Specification at page 1, line 27 to page 2, line 2; page 2, lines 24–28; page 3, lines 1–10; and original claim 9.

Therefore, Applicant submits that the specification satisfies the written description because it describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention by using a description of the claimed method that fully set forth the claimed invention. M.P.E.P. § 2163.

In view of the foregoing, Applicant respectfully requests withdrawal of this rejection.

35 U.S.C. § 103(a) — Obviousness

Claim 1 stands rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent Application Publication No. 2002/0177545 ("Donovan") in view of Andreyko, *et al.* (1986) "Treatment of hirsutism with a gonadotropin-releasing hormone agonist (Nafarelin)," *Journal of Clinical Endocrinology & Metabolism* 63: 854–859 ("Andreyko"). To the extent applied against the claims as amended, Applicant respectfully traverses this rejection.

As noted above, claim 1 has been amended to recite a "method for reducing hair growth in a female patient suffering from hirsutism comprising injecting an effective amount of botulinum toxin type A to the area situated between the lips and the nose of said patient." Further, new claim 19 recites "[a] method for reducing hair growth in a female patient suffering from hirsutism comprising shaving an area of skin on said patient followed by injecting an effective amount of botulinum toxin type A to the shaved area." The Office Action asserts that the combination of Donovan and Andreyko renders the claimed invention obvious. Office Action at page 6. Applicant respectfully submits that the claims, as amended, are patentable over Donovan and Andreyko, either taken alone or in combination for the following reasons.

The Donovan Reference:

Donovan discloses the administration of botulinum toxin fragments conjugated to gonadotropin-releasing hormone (*e.g.*, LH_N-GnRH, herein "GnRH conjugate") via direct *injection into the central nervous system* (*e.g.*, intraspinal and intracranial injection) to treat gonadotropin related illnesses. Donovan at ¶¶ 79, 80, 95, and 112 (emphasis added). Alternatively, Donovan discloses "[o]ther routes of administration" including "transdermal, peritoneal, subcutaneous, intramuscular, intravenous, and intrarectal" in a manner calculated to "pass through the blood brain barrier to reach its target site." Donovan at ¶ 113. Donovan only discloses treating medical conditions that may benefit from a decrease in the gonadotropin levels in the body. *Id.* at ¶¶ 69, 109, 112, and 113. For example, Donovan focuses on treatment of endometriosis, pancreatic cancer, prostate cancer, precocious puberty, endometrial cancer, breast cancer. *Id.* at Examples 1–5; claims 23 and 24. Indeed, Donovan only mentions hirsutism in the Background section, noting that GnRH agonists and antagonists had been used to treat hirsutism. *Id.* at ¶ 9.

Citing paragraphs 53 and 113, the Office Action incorrectly concludes that Donovan discloses "local administration of the pharmaceutical [(*i.e.*, GnRH conjugate)] at or to the vicinity within an animal body to provide a therapeutic effect." Donovan only discloses treating medical conditions that may benefit from a decrease in the gonadotropin levels in the body. *Id.* at ¶¶ 69, 109, 112, and 113. Gonadotropin is a hormone released from the pituitary gland. While Applicant acknowledges that Donovan does include a paragraph defining "local administration" at paragraph 53, nowhere does Donovan state that his GnRH conjugate is administered by local administration other than by injection into the pituitary gland. Further, paragraph 153 specifically states that the agent must "pass through the blood brain barrier to reach its target site." This is not local administration at or to the vicinity to provide a therapeutic effect. Rather, Donovan merely suggests using different systemic routes of administration to deliver the drug to the central nervous system if the drug is not injected directly into the pituitary or brain. Applicant respectfully submits that the Office Action is incorrect in concluding that Donovan discloses local administration of the GnRH conjugate at or to the vicinity within an animal body to provide a therapeutic effect. Therefore, the present claims differ from Donovan by requiring

"injecting...to the area situated between the lips and the nose" or "injecting...to the shaved area."

Further, Donovan does not disclose that "botulinum toxin type A" as claimed is effective for treatment of gonadotropin related illnesses. Rather, Donovan discloses administration of a GnRH conjugate that includes light chain components or fragments derived from botulinum toxin, but does not disclose administration of botulinum toxin type A to treat gonadotropin related illnesses. The Office Action appears to acknowledge that the GnRH conjugate comprises a conjugate of "light chain component or a fragment thereof a botulinum toxin; a translocation component comprising a heavy chain or a modified heavy chain of a botulinum toxin; and a targeting component which selectively binds to a GnRH receptor." Office Action at page 6. Indeed, botulinum toxin A lacks at least the "targeting component" that is required for Donovan's GnRH conjugate to "bind to a specific target cell receptor." Donovan at ¶ 87. Applicants also submit that botulinum toxin type A is not a gonadotropin agonist or antagonist, the class of agents disclosed by Donovan to be useful in treating gonadotropin related illnesses. *See* Donovan at ¶ 9. Therefore one of ordinary skill in the art would not consider botulinum toxin type A itself as useful in treating gonadotropin related illnesses. Indeed, it is notoriously well established under 35 U.S.C. § 103 that a modification which would undermine the operability of a reference is the very antithesis of obviousness for the very reason that one of ordinary skill in the art would not effect a modification if it would render a teaching ineffective. Here, the rejection proferred by the Patent Office does just that--it would require that one of ordinary skill in the art, to arrive at the claimed invention, modify the teachings of Donovan so as to undermine Donovan's operability.

The Andreyko Reference:

Andreyko discloses the systemic administration of Nafarelin, a superactive agnostic GnRH analog which lowers the serum level of androgens, to treat hirsutism in women. Andreyko at Abstract, page 855. Andreyko is completely unrelated to, and contains no disclosure of, botulinum toxin, much less botulinum toxin type A as claimed. Further, Andreyko confirms that GnRH analogs do not affect hirsutism by local injection at the site of hair growth. Rather, Andreyko is clear that Nafarelin has a systemic effect and accordingly discloses systemic routes

of Nafarelin administration, such as inhalation (nasal spray). The current claims, which recite, among other limitations, "injecting...to the area situated between the lips and the nose" or "injecting...to the shaved area," are incompatible with systemic administration.

The Combination of Donovan and Andreyko:

The Office Action correctly acknowledges that "[Donovan] does not specifically teach using [Donovan's botulinum-fragment-containing GnRH analog] to reduce downy hair growth in a patient suffering from hirsutism." Office Action at page 6. To remedy this deficiency, the Office Action cites Andreyko's agonistic GnRH analog, Nafarelin, used to the treat of hirsutism. Office Action at pages 6–7. Applicant respectfully submits that a person who combines Donovan and Andreyko as alleged in the Office Action would administer the GnRH binding conjugate of Donovan, in the manner taught by Donovan (or Andreyko), to treat hirsutism. However, Applicant respectfully submits that this procedure would have failed to result in administering "botulinum toxin type A" and/or "injecting...to the area situated between the lips and the nose" or "injecting...to the shaved area" as recited in the amended claims.

As noted above, Donovan does not disclose administration of botulinum toxin type A and instead administers a targeted conjugate containing a "light chain component or a fragment thereof a botulinum toxin; a translocation component comprising a heavy chain or a modified heavy chain of a botulinum toxin; and a targeting component which selectively binds to a GnRH receptor." The claims require "botulinum toxin type A" and not "botulinum toxin" generally. Thus, the conjugate of Donovan, which includes only fragments of botulinum toxin, fails to meet the claimed "botulinum toxin type A" limitation. Andreyko fails to cure this deficiency as it merely discloses systemic administration of Nafarelin to treat hirsutism, and is completely silent as to botulinum toxin, much less "botulinum toxin type A" as claimed. Since the cited references, taken together, do not meet every limitation of the claimed invention, the obviousness rejection is improper and must be withdrawn.

The amended claims now recite, among other limitations, "injecting...to the area situated between the lips and the nose" or "injecting . . . to the shaved area." Neither Donovan nor Andreyko disclose that GnRH analogs would directly affect hair follicles or have any effect at the point of unwanted hair growth. Instead, the combined disclosure of Donovan and Andreyko

would in fact suggest administration in a manner that lowers the serum levels of androgens in women suffering from hirsutism. The Office Action admits that neither Donovan nor Andreyko discloses administering GnRH conjugate to the upper lip of a hirsutism patient. To address this deficiency, the Office Action concludes that it would have been customary for an artisan of ordinary skill to determine the optimal route and site of administration to best achieve the desired results. Office Action at pages 8–9.

Applicant respectfully submits that this obviousness rationale is flawed. First, the Office Action fails to address the incompatibility "injecting...to the area situated between the lips and the nose" or "injecting . . . to the shaved area" with the systemic administration of GnRH analogs to treat hirsutism allegedly suggested by the combination of Donovan and Andreyko. In fact, neither of these references suggests that a GnRH analog could affect hair growth at the site of administration. Second, Applicant submits that only result-effective variables can be optimized, thus a particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 U.S.P.Q. 6 (CCPA 1977); *See also In re Boesch*, 617 F.2d 272, 205 U.S.P.Q. 215 (CCPA 1980). The Office Action fails to establish that the claimed administration methods could be used to introduce the GnRH analog of Donovan to reduce systemic levels of androgen as suggested by Andreyko. Again, neither reference suggests a GnRH analog would have had any activity at the site of administration. Indeed, the specification discloses that unwanted hair growth can be reduced by injecting botulinum toxin type A at the site of unwanted hair growth without the use of a GnRH analog.

New claims 17, 18, 27, and 28 are drawn to botulinum toxin types A1 and A2, neither of which are disclosed by Donovan or Andreyko. Claims 13–16 and 23–26 are drawn to dosages of botulinum toxin which are not disclosed by either Donovan or Andreyko. Finally, claims 20–22 are drawn to areas treated by the claimed method which are not disclosed by Donovan or Andreyko.

In view of the foregoing, Applicant respectfully requests withdrawal of this rejection.

Claims 1, 11, and 12 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Donovan and Andreyko in view of Cedars-Sinai Medical Center: Hirsutism (September 2002) ("Cedars-Sinai"). To the extent applied to the claims as amended, Applicant respectfully traverses this rejection.

As discussed above, the cited combination of Donovan and Andreyko fails to suggest administering "botulinum toxin type A" and/or "injecting...to the area situated between the lips and the nose" or "injecting...to the shaved area" as recited in the amended claims. Applicant respectfully submits that Cedars-Sinai fails to cure these deficiencies of Donovan and Andreyko. The Cedars-Sinai publication is drawn to a discussion of hirsutism and its treatment. Cedars-Sinai at page 1. The treatments for hirsutism disclosed by Cedars-Sinai include hormonal treatment (*e.g.*, birth control pills), anti-androgen drugs (*e.g.*, spironolactone), an electrolysis, laser removal, and a facial cream comprising eflornithine HCl. *Id.* at pages 2–4. As with Andreyko, Cedars-Sinai is completely silent as to administration of botulinum toxin, and is in complete agreement with Andreyko that hirsutism was known to be treated by reduction of androgens. Given that hirsutism was known to be treated by administration of GnRH analogs to reduce systemic androgen levels, there is no reason that a person having ordinary skill in the art would have tried administering botulinum toxin type A by "injecting ...to the area situated between the lips and the nose" or "injecting...to the shaved area" as recited in the amended claims. Accordingly, Applicant submits that Donovan, Andreyko, Cedars-Sinai, alone or in any combination do not disclose the botulinum toxin of claim 1, the condition, nor the area targeted in treatment.

Applicant also submits that newly added claims 17, 18, 27, and 28 are drawn to botulinum toxin types A1 and A2, neither of which are disclosed by Donovan, Andreyko, or Cedars-Sinai. Claims 13–16 and 23–26 are drawn to dosages of botulinum toxin which are not disclosed by Donovan, Andreyko, or Cedars-Sinai. Finally, claims 20–22 are drawn to areas treated by the claimed method which are not disclosed by Donovan, Andreyko, or Cedars-Sinai.

In view of the foregoing, Applicant respectfully requests withdrawal of this rejection.

CONCLUSION

In view of the above remarks, early notification of a favorable consideration is respectfully requested. An indication of allowance of all claims is respectfully requested.

Respectfully submitted,
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